COMPARISON OF VIRTUAL ENDOSCOPY AND TRANSABDOMINAL ULTRASONOGRAPHY WITH CONVENTIONAL ENDOSCOPY IN PATIENTS WITH HAEMATURIA

Dissertation submitted to

THE TAMILNADU Dr. M. G. R. MEDICAL UNIVERSITY

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MCh. UROLOGY

BRANCH IV

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FORWARDING CERTIFICATE

We solemnly declare that this dissertation "**COMPARISON OF VIRTUAL ENDOSCOPY AND TRANSABDOMINAL ULTRASONOGRAPHY WITH CONVENTIONAL ENDOSCOPY IN PATIENTS WITH HAEMATURIA"** was prepared by the candidate in the Department of Urology, Madras Medical College and Government General Hospital, Chennai under the guidance and supervision of Professor and HOD Department of Urology, Madras Medical College and Government General Hospital, Chennai between 2007 – 2010.

This dissertation is forwarded to the Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the University requirements for the award of the degree of MCh Urology.

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DECLARATION

I solemnly declare that this dissertation "**COMPARISON OF VIRTUAL ENDOSCOPY AND TRANSABDOMINAL ULTRASONOGRAPHY WITH CONVENTIONAL ENDOSCOPY IN PATIENTS WITH HAEMATURIA"** was prepared by me in the Department of Urology, Madras Medical College and Government General Hospital, Chennai under the guidance and supervision of Professor and HOD Department of Urology, Madras Medical College and Government General Hospital, Chennai between 2007 – 2010.

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CONTENTS

INTRODUCTION

Main aim of haematuria evaluation in patients is to diagnose Urothelia cancer. The incidence of urothelial cancer in patients with haematuria is 6 to 12 %. Most of the urothelial cancer are from the bladder, upper tract tumor incidence is only 0.5 %.

Patients with haematuria can be of two types

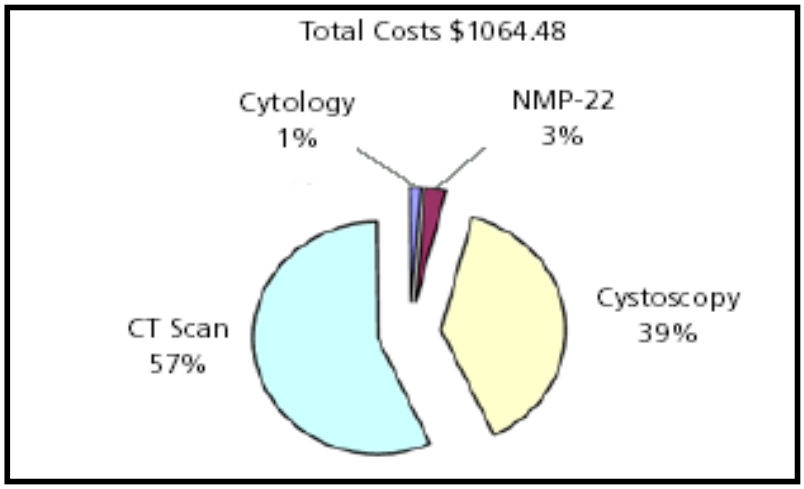
1. Visible haematuria otherwise known as gross haematuria
2. Microscopic haematuria. Defined as more than 3 RBCs per high power field

Patients with gross haematuria have higher incidence of (30 percent) urothelial cancer.

Currently recommended investigations for haematuria evaluation are

1. CT of the abdomen and pelvis (As it is more superior to IVU and Ultrasound in detecting lesions)
2. Urine cytology for malignant cells and
3. Cystoscopy

Boback et al in his study made a cost estimation for haematuria evaluation and the sensitivity of the investigations done. The highlights of the study is presented below :



The study by Boback *et al* has shown that the cost of evaluation of haematuria is around 1000 dollars, which is a significant amount to be spent on each patient. Main bulk of the cost is due to the CT imaging and cystoscopy. CT evaluation cannot be avoided as it is essential for detecting lesions other than the urothelial tumors like stone disease and renal cell carcinoma.

So attention was focused on alternative methods other than cystoscopy to rule out bladder tumors which will cut down the cost of evaluation dramatically.

Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Cytology	27% (12-48%)	100% (99-100%)	100%	95%
NMP-22	73% (52-88%)	76% (71-80%)	19%	97%
Cystoscopy	96% (79-97%)	97% (95-99%)	74%	99%
CT Urogram	62% (41-80%)	98% (96-99%)	67%	97%
All Four Tests	100% (87-100%)	74% (69-78%)	22%	100%

Currently cystoscopy is the ‘gold standard’ to rule out that the patient is not having a bladder lesion to account for the haematuria. Because it can be seen in the above table from the study by Boback et al CT (62 %) and cytology (27 %) are not as sensitive as Cystoscopy.

This led the search of cost effective but highly sensitive modalities which are as sensitive as cystoscopy . This has resulted in two modalities in the horizon:

1. Molecular markers in urine

2. Virtual cystoscopy

Similar to cystoscopy virtual evaluation of the upper tracts can also be done to rule out urothelial tumors named as virtual ureteroscopy and virtual nephroscopy. Collectively virtual cystoscopy, ureteroscopy and nephroscopy are called as Virtual endoscopy

Virtual endoscopy (VE) is a 3D computer rendering technique with the possibility of interactive intraluminal navigation within the bladder simulating a conventional endoscopy

VE is possible with the routine CT images which we do for patients with haematuria when the software is available so there is no added cost to the patient.

Virtual imaging is possible by the Marching cubes algorithm which is used to delineate the mucosa. It is based on the change in the attenuation values between the fluid (contrast filled urine) in the bladder lumen and the bladder wall. This results in a 3D representation of the mucosal surface. The computer mouse can be moved within the lumen as if we move the endoscope within the bladder and ureter and the entire mucosa examined systematically in an interactive manner.

(Lorensen WE, Clic HE. Marching cubes:a high resolution 3D surface construction algorithm. Comput Graph 1987; 21:163 – 9)

AIM AND OBJECTIVE

To compare virtual endoscopy (VE) and Trans-abdominal ultrasound with Conventional cystoscopy (CC), in the detection of bladder tumors in patients with haematuria.

REVIEW OF LITERATURE

To visualize the renal pelvis and ureter the delayed CECT images are sufficient. But to visualize the bladder is a bit difficult.

To apply the marching cubes algorithm there must be a good attenuation gradient between the bladder lumen and the mucosa.Based on the virtual endoscopic examination of the para nasal sinuses and tracheobronchial tree where the air in the passages offered good attenuation gradient initial virtual cystoscopic examination was based on carbondioxide insufflation of bladder.

Filling the bladder with gas also allows good attenuation gradient between the lumen and the mucosa. Even virtual colonoscopy is possible by insufflating carbon di oxide in the colon.

So Virtual cystoscopy had been initially attempted by filling bladder with 300 ml of carbon dioxide by **Vining et al** and also by others like **Noriasu et al**, the problem is the bladder continuously forms urine and urine stays in the bladder base and carbon di oxide floating above. As urine doesn’t offer good attenuation gradient the lesions in the bladder base were missed. For these reasons contrast cystogram is superior for virtual endoscopic evaluation of bladder.

To ensure a good attenuation gradient between the lumen and mucosa diluted contrast must be present in the bladder. To achieve this catheter was introduced in the bladder and urine drained followed by contrast instillation into the bladder as done by **Roberto iglesias et al.**

Or an infant feeding tube can also be used for contrast instillation as done by **Kishore et al.** The smaller caliber of the infant feeding tube produces little discomfort than a catheter.

But still these are invasive methods as it is similar to introducing a small size flexible cystoscope and are not truly non - invasive.

Merkle et al Showed that it is feasible to create VC after an intravenous injection with contrast media.

Similar VC studies using intra venous contrast was done by **Thiagarajan nambirajan et al.**

So we did not insert catheter into the bladder as it itself is invasive. We waited for 30 minutes for the contrast to fill the bladder. During the waiting period we made the patient ambulant so that there is no gravitation of the contrast and ensured mixing of contrast well with urine. Those patients on a stretcher were moved to right and left lateral positions repeatedly. Screening cystogram was done to make sure that a dense homogenous cystogram was present before 64 slice bladder imaging.

The original multislice CT devices had four rows of detectors, but recent multislice CT devices which are produced by several manufacturers, comprise a single rotating X-ray tube that provides a beam of photons travelling through the patient, and which are then received by multiple rows of detectors, thus effectively producing multiple slices for each rotation of the X-ray tube. These multislice CT devices produce more refined three dimensional images, and are increasingly used in coronary angiography and virtual endoscopy.

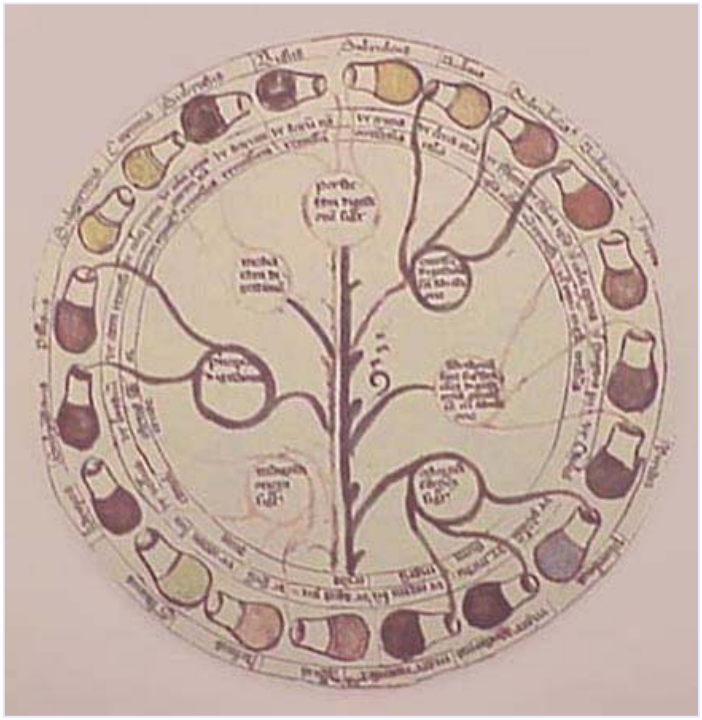
Noriyasu Kawai et al have used 16 slice CT for VC Intravenous urography-virtual cystoscopy is a better preliminary examination than air virtual cystoscopy

We have used 64 slice CT in our study which we thought will improve the diagnostic ability

If CT-based VC has enough sensitivity, this combined with CT urography could potentially be a single, noninvasive screening investigation for haematuria. This could replace the current use of combined cystoscopy (CC) and upper tract assessment with CT urogram .

We assessed the feasibility and efficacy of CT based VC and compared it with conventional cystoscopy (CC), using intravenous contrast media, thereby avoiding catheterization and 64 slice CT to enhance sensitivity

HAEMATURIA EVALUATION



Blood in the urine (haematuria) can originate from any site along the urinary tract and, whether gross or microscopic, may be sign of serious underlying disease, including malignancy. Overall the incidence of urothelial cancer in patients with haematuria is around 6 – 12 %. The literature agrees that gross haematuria warrants a thorough diagnostic evaluation as the incidence of urothelial cancer is high (30 %). In microscopic hematuria the incidence reported is variable .Mayo clinic reports on analyzing 2000 patients that only 0.5 % had a urologic malignancy and 1.8 % developed other serious urologic diseases within 3 years after identification of of haematuria (Mohr et al, 1986) .Conversely investigators at the University of Wisconsin found that 26 % of adults who had at least one positive dipstick reading for haematuria were subsequently found to have significant urologic pathology (Messing et al , 1987). This variation may be due to the presence of patients of varying risk for disease in the study groups. So patients were classified into high risk and low risk groups to further evaluate microscopic haematuria. High risk patients with microscopic haematuria have an urothelial cancer risk of 30 %and hence a complete work up is indicated. Whereas only limited work up is indicated in low risk patients. And another issue is whether physicians should test for haematuria in asymptomatic patients remains at issue. No major organization currently recommends screening for microscopic hematuria in asymptomatic adults.

The initial determination of microscopic hematuria should be based on microscopic examination of urinary sediment from a freshly voided, clean-catch, midstream urine specimen. Hematuria can be measured quantitatively by any of the following:

(1) Determination of the number of red blood cells per milliliter of urine excreted (chamber count)

(2) Direct examination of the centrifuged urinary sediment (sediment count)

(3) Indirect examination of the urine by dipstick (the simplest way to detect microscopic haematuria).

Given the limited specificity of the dipstick method (65 percent to 99 percent for two to five red blood cells per high-power microscopic field), however the sensitivity is over 90 % , the initial finding of microscopic haematuria by the dipstick method should be confirmed by microscopic evaluation of urinary sediment.

The recommended definition of microscopic hematuria is three or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens. To account for intermittent positive tests for haematuria in patients with urologic malignancies, one group of investigators proposed that patients with more than three red blood cells per high-power field from two of three properly collected

urine specimens should be considered to have microhaematuria and, thus, should be evaluated appropriately. However, before a decision is made to defer evaluation in patients with one or two red blood cells per high-power field, risk factors for significant disease should be taken into consideration. High-risk patients should be considered for full urologic evaluation after one properly performed urinalysis documenting the presence of at least three red blood cells per high-power field.

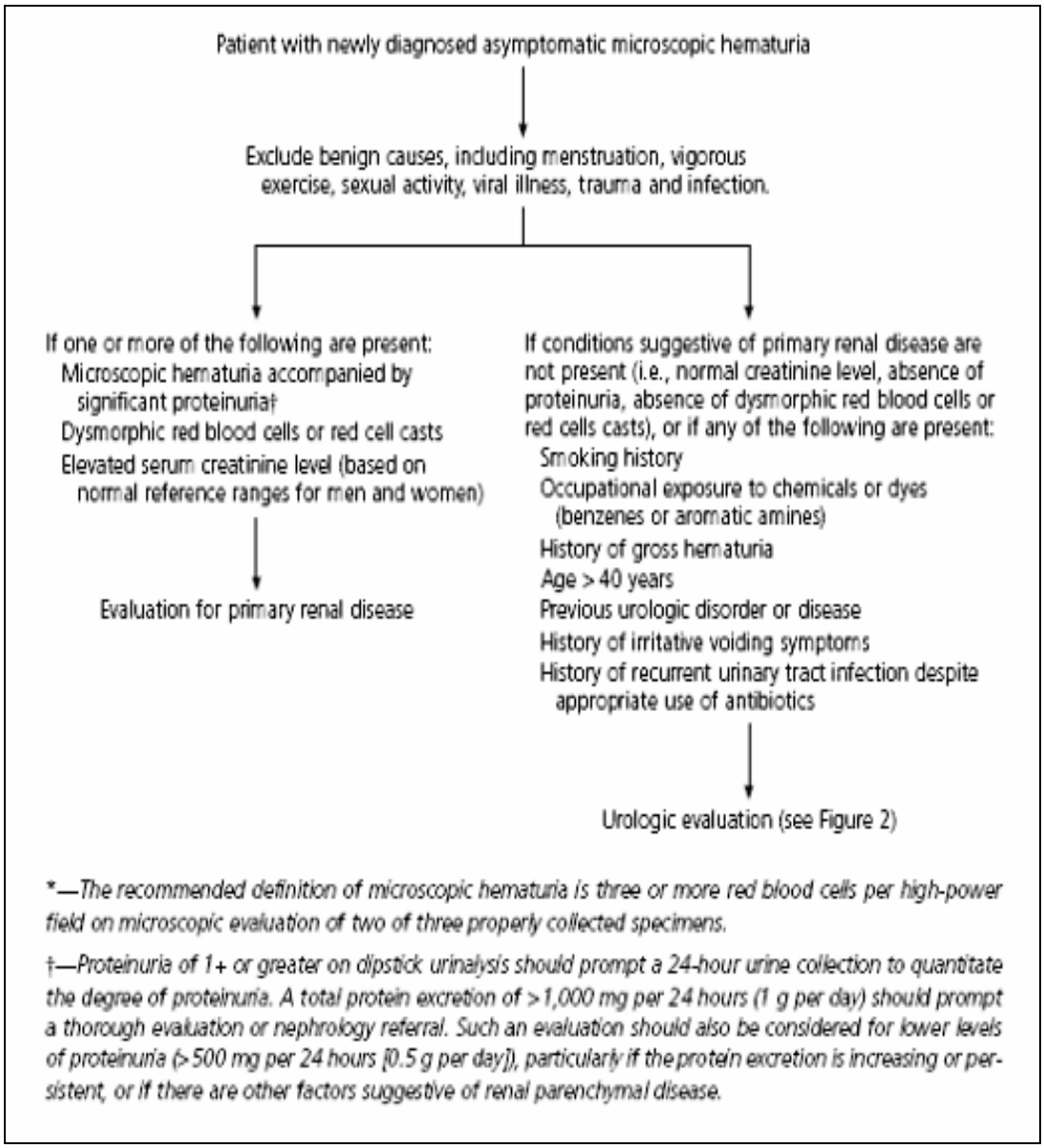
Risk Factors for Significant Disease in Patients with Microscopic Hematuria

1. Smoking history
2. Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
3. History of gross hematuria
4. Age >40 years
5. History of urologic disorder or disease
6. History of irritative voiding symptoms
7. History of urinary tract infection
8. Analgesic abuse
9. History of pelvic irradiation

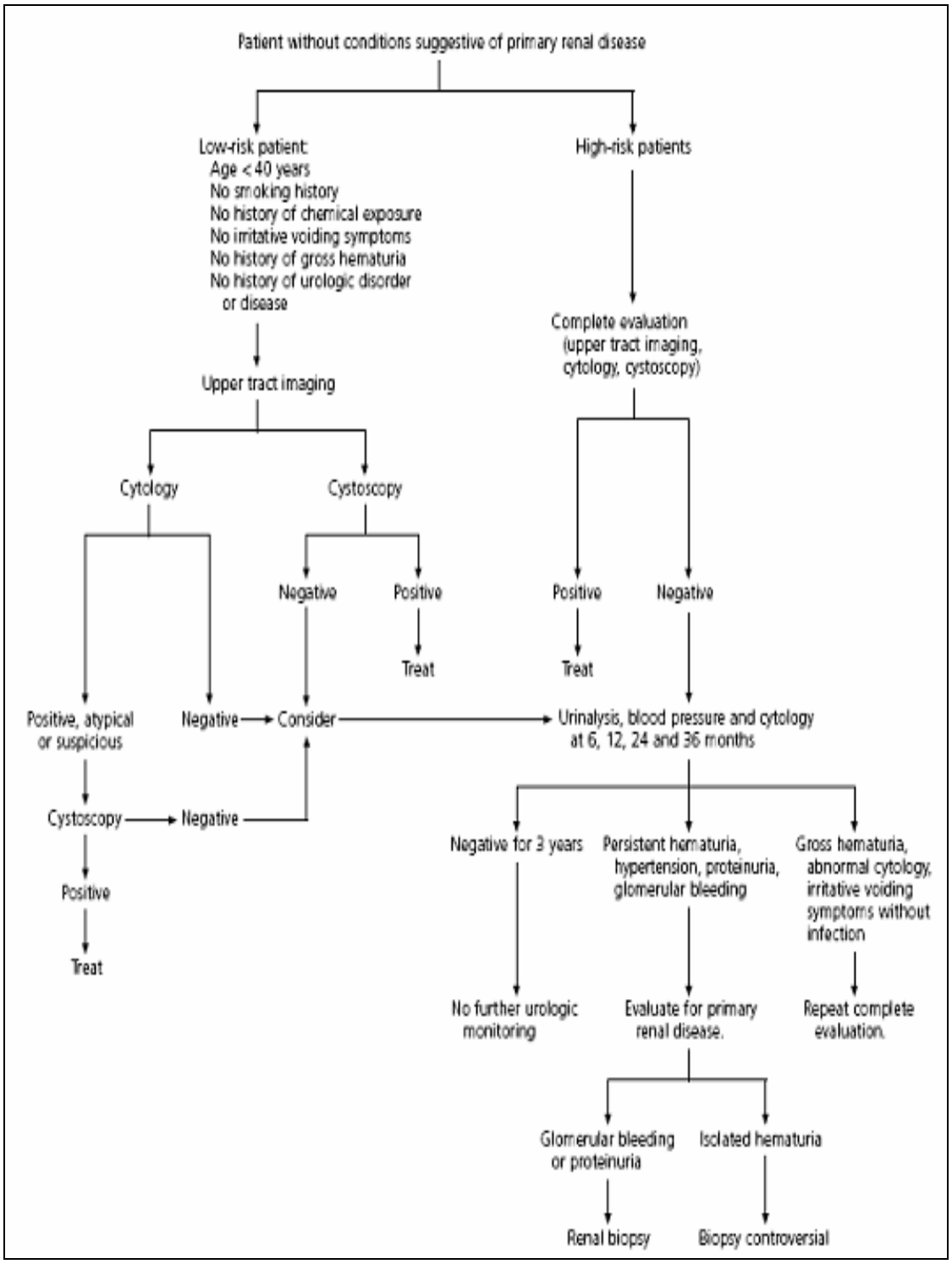
The prevalence of microscopic haematuria varies from 0.19 percent to as high as 21 percent. In five population-based studies, the prevalence of asymptomatic microscopic haematuria varied from 0.19 percent to 16.1 percent.

Differences in the age and sex of the populations screened, the amount of follow-up and the number of screening studies per patient account for this range. In older men, who are at a higher risk for significant urologic disease, the prevalence of microscopic haematuria was as high as 21 percent.

Patients with microscopic haematuria who are at risk for urologic disease or primary renal disease should undergo an appropriate evaluation. In patients at low risk for disease, some components of the evaluation may be deferred. An algorithm for the initial evaluation of newly diagnosed microscopic haematuria is provided below.



An approach to the urologic evaluation of patients without conditions suggestive of primary renal disease is presented in the algorithm below.


Patient without conditions suggestive of primary renal disease
Low-risk patient:
Age < 40 years
No smoking history
No history of chemical exposure
No irritative voiding symptoms
No history of gross hematuria
No history of urologic disorder or disease
High-risk patients
Upper tract imaging
Complete evaluation (upper tract imaging, cytology, cystoscopy)
Cytology
Cystoscopy
Negative
Positive
Positive
Negative
Treat
Treat
Positive, atypical or suspicious
Negative
Consider
Urinalysis, blood pressure and cytology at 6, 12, 24 and 36 months
Cystoscopy
Negative
Positive
Treat
Negative for 3 years
Persistent hematuria, hypertension, proteinuria, glomerular bleeding
Gross hematuria, abnormal cytology, irritative voiding symptoms without infection
No further urologic monitoring
Evaluate for primary renal disease.
Repeat complete evaluation.
Glomerular bleeding or proteinuria
Isolated hematuria
Renal biopsy
Biopsy controversial

The presence of significant proteinuria, red cell casts or renal insufficiency or a predominance of dysmorphic red blood cells in the urine should prompt an evaluation for renal parenchymal disease or referral to a nephrologist. Significant proteinuria is defined as a total protein excretion of greater than 1,000 mg per 24 hours (1 g per day), or greater than 500 mg per 24 hours (0.5 g per day) if protein excretion is persistent or increasing or if other factors suggest the presence of renal parenchymal disease. In the absence of massive bleeding, a total protein excretion in excess of 1,000 mg per 24 hours would be unlikely and should prompt a thorough evaluation or nephrology referral. Red cell casts are virtually pathognomonic for glomerular bleeding. Unfortunately, they are a relatively insensitive marker. Therefore, it is useful to examine the character of the red blood cells.25 Dysmorphic urinary red blood cells show variation in size and shape and usually have an irregular or distorted outline. Such red blood cells are generally glomerular in origin. In contrast, normal doughnut shaped red blood cells are generally due to lower urinary tract bleeding. Accurate determination of red blood cell morphology may require inverted phase contrast microscopy.

The percentage of dysmorphic red blood cells required to classify haematuria as glomerular in origin has not been adequately defined. In general, glomerular bleeding is associated with more than 80 percent dysmorphic red blood cells, and lower urinary tract bleeding is associated with more than 80 percent normal red blood cells. Percentages falling between these ranges are indeterminate and could represent bleeding from either source.

The initial evaluation of the urinary sediment generally identifies patients with parenchymal renal disease.4 Glomerular disease is most likely in this setting and may be associated with a variety of systemic diseases, including lupus erythematosus, vasculitis, malignancy and infections such as hepatitis and endocarditis. Glomerular diseases localized to the kidney include membranoproliferative glomerulonephritis, IgA nephropathy and crescentic glomerulonephritis. In addition, interstitial renal disease, such as drug induced interstitial disease or analgesic nephropathy, may be associated with haematuria. If systemic causes are not identified, renal biopsy is usually recommended.

Patients with microscopic haematuria, a negative initial urologic evaluation and no evidence of glomerular bleeding are considered to have isolated hematuria. Although many such patients may have structural glomerular abnormalities, they appear to have low risk for progressive renal disease. Thus, the role of renal biopsy in this setting has not been defined. Nevertheless, because follow-up data are limited, these patients should be followed for the development of hypertension, renal insufficiency or proteinuria. In patients without risk factors for primary renal disease, a complete urologic evaluation should be performed. Complete urologic evaluation of microscopic hematuria includes a history and physical examination, laboratory analysis and radiologic imaging of the upper urinary tract followed by cystoscopic examination of the urinary bladder. In some instances, cytologic evaluation of exfoliated cells in the voided urine specimen may also be performed. If a careful history suggests a potential “benign” cause

for microscopic hematuria the patient should undergo repeat urinalysis 48 hours after cessation of the activity (i.e., menstruation, vigorous exercise, sexual activity or trauma). No additional evaluation is warranted if the hematuria has resolved. Patients with persistent hematuria require evaluation.

In women, urethral and vaginal examinations should be performed to exclude local causes of microscopic hematuria. A catheterized urinary specimen is indicated if a clean catch specimen cannot be reliably obtained (i.e., because of vaginal contamination or obesity). In uncircumcised men, the foreskin should be retracted to expose the glans penis, if possible. If a phimosis is present, a catheterized urinary specimen may be required. The laboratory analysis begins with comprehensive examination of the urine and urinary sediment. The number of red blood cells per high-power field should be determined. In addition, the presence of dysmorphic red blood cells or red cell casts should be noted.

The urine should also be tested for the presence and degree of proteinuria and for evidence of urinary tract infection. Patients with urinary tract infection should be treated appropriately, and urinalysis should be repeated six weeks after treatment. If the hematuria resolves with treatment, no additional evaluation is necessary. Serum creatinine should be measured. The remaining laboratory investigation should be guided by specific findings of the history, physical examination and urinalysis. Urothelial cancers, the target of a cytologic examination, are the most commonly detected malignancies in patients with microscopic haematuria.

Voided urinary cytology is recommended in all patients who have risk factors for transitional cell carcinoma.This test can be a useful adjunct to cystoscopic evaluation of the bladder, especially in the determination of carcinoma in situ. In patients with microscopic haematuria who do not have risk factors for transitional cell carcinoma, urinary cytology or cystoscopy may be used. If cytology is chosen and malignant or atypical/suspicious cells are identified, cystoscopy is required because the presence of haematuria is a significant risk factor for malignancy in such patients.

Several recently identified voided urinary markers have been examined for the early detection of bladder cancer. At this time, insufficient data are available to recommend their routine use in the evaluation of patients with microscopic hematuria. Further studies are warranted to determine the role of these markers in the diagnostic evaluation of such patients. Intravenous urography, ultrasonography and computed tomography are used to evaluate the urinary tract in patients with microscopic hematuria. Because of lack of impact data, evidence-based imaging guidelines cannot be formulated. In patients with microscopic hematuria, imaging can be used to detect renal cell carcinoma, transitional cell carcinoma in the pelvicaliceal system or ureter, urolithiasis and renal infection. Table below highlights imaging modalities used to evaluate the urinary tract.

Imaging Modalities for Evaluation of the Urinary Tract

Modality	*Advantages and disadvantages*
Intravenous urography	Considered by many to be best initial study for evaluation of urinary tract
	Widely available and most cost-efficient in most centers
	Limited sensitivity in detecting small renal masses
	Cannot distinguish solid from cystic masses; therefore, further lesion characterization by ultrasonography, computed tomography or magnetic resonance imaging is necessary
	Better than ultrasonography for detection of transitional cell carcinoma in kidney or ureter
Ultrasonography	Excellent for detection and characterization of renal cysts
	Limitations in detection of small solid lesions (< 3 cm)
Computed tomography	Preferred modality for detection and characterization of solid renal masses
	Detection rate for renal masses comparable to that of magnetic resonance imaging, but more widely available and less expensive
	Best modality for evaluation of urinary stones, renal and perirenal infections, and associated complications
	Sensitivity of 94% to 98% for detection of renal stones, compared with 52% to 59% for intravenous urography and 19% for ultrasonography

Intravenous urography (IVU) has traditionally been the modality of choice for imaging the urinary tract, and many still consider it to be the best initial study for the evaluation of microhematuria. However, IVU by itself has limited sensitivity in detecting small renal masses. When a mass is detected by IVU, further lesion characterization by ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) is necessary because IVU cannot distinguish solid from cystic masses. CT is the best imaging modality for the evaluation of urinary stones, renal and perirenal infections, and associated complications. For the detection of transitional cell carcinoma in the kidney or ureter, IVU is superior to ultrasonography. CT urography with abdominal compression results in reliable opacification of the collecting system,

comparable to that obtained with IVU. High detection rates for transitional cell carcinoma on contrast-enhanced CT images have been reported, but the studies offer no statistical analysis.There are currently no studies comparing the performance of various diagnostic- imaging modalities in the detection of transitional cell carcinomas in the upper urinary tract. Retrograde pyelography is considered the best imaging approach for the detection and characterization of ureteral abnormalities, but this general opinion is not based on evidence. No data exist showing the impact of IVU, ultrasonography, CT or MRI on the management of patients with microscopic hematuria. Therefore, evidence-based imaging guidelines cannot be formulated. If CT is chosen as the initial upper tract study, the imaging protocol should be adapted to the diagnostic goals, such as the exclusion of urolithiasis and renal neoplasm. CT urography spiral (helical) is preferred if the technology is available. Neither oral nor rectal contrast medium is required. The CT protocols should start with a noncontrast scan. If this scan demonstrates urolithiasis in a patient who is at low risk for underlying malignancy no further scanning is needed. In all other patients, including those in whom a urinary calculus is not detected, intravenous contrast medium should be injected. CT scout (topogram) or plain-film abdominal radiography (depending on the equipment available) can be performed at the end of the CT examination to assess the ureters and bladder in an IVU–like fashion. Even better is multiplanar reconstruction of the available source images.

Cystoscopic evaluation of the bladder (complete visualization of the bladder mucosa, urethra and ureteral orifices) is necessary to exclude the presence of bladder cancer.

Cystoscopy as a component of the initial office evaluation of microscopic hematuria is recommended in all adult patients more than 40 years of age and in patients less than 40 years of age with risk factors for bladder cancer. This includes patients in whom upper tract imaging reveals a potentially benign source for bleeding. Cystoscopy appears to have a low yield in select patients at low risk for bladder cancer, including men and women younger than 40 years with no risk factors for this malignancy.In these patients, initial cystoscopy may be deferred, but urinary cytology should be performed. Initial diagnostic cystoscopy can be performed under local anesthesia using a rigid or flexible cystoscope. Compared with rigid cystoscopy, flexible cystoscopy causes less pain and is associated with fewer post-procedure symptoms.In addition, positioning and preparation of the patient are simplified, and procedure time is reduced. Flexible cystoscopy appears to be at least equivalent in diagnostic accuracy to rigid cystoscopy; for some lesions (i.e., those at the anterior bladder neck), it may be superior.

Because some patients with a negative initial evaluation for microhaematuria eventually develop significant urologic disease, some form of follow-up is indicated. Although most patients with a negative initial evaluation for microhaematuria do not develop significant urologic disease,

some patients do. Consequently, some form of follow-up is indicated. Because the appearance of haematuria can precede the diagnosis of bladder cancer by many years, such follow-up seems especially important in high- risk groups, including patients older than 40 years and those who use tobacco or whose occupational exposures put them at risk.Because the risk of life-threatening lesions in patients with a negative initial evaluation is low and the data regarding follow-up in such patients are sparse, recommendations regarding appropriate follow-up must be based on consensus opinion, in addition to review of the available literature-based evidence. In patients with a negative initial evaluation of asymptomatic microscopic haematuria, consideration should be given to repeating urinalysis, voided urine cytology and blood pressure determination at six, 12, 24 and 36 months.

Although cytology may not be a sensitive marker for detecting low-grade transitional cell carcinoma, it detects most high-grade tumors and carcinomas in situ, particularly if the test is repeated. Such high-grade lesions are the most likely to benefit from early detection.

Additional evaluation, including repeat imaging and cystoscopy, may be warranted in patients with persistent hematuria in whom there is a high index of suspicion for significant underlying disease. In this setting, the clinical judgment of the treating physician should guide further evaluation. Immediate urologic reevaluation, with consideration of cystoscopy, cytology or repeat imaging, should be performed if any of the following occur: (1) gross

hematuria, (2) abnormal urinary urinary cytology or (3) irritative voiding symptoms in the absence of infection. If none of these occurs within three years, the patient does not require further urologic monitoring. Further evaluation for renal parenchymal disease or referral to a nephrologist should be considered if hematuria persists and hypertension, proteinuria or evidence of glomerular bleeding (red cell casts, dysmorphic red blood cells) develops.

UROTHELIAL CARCINOMA

Carcinoma in Situ

Carcinoma in situ may appear as a velvety patch of erythematous mucosa, although quite often it is endoscopically invisible. Histologically, it consists of poorly differentiated TCC confined to the urothelium .Carcinoma in situ may be asymptomatic or may produce severe symptoms of urinary frequency, urgency, and dysuria (Utz et al, 1970 ; Utz and Farrow, 1984). Urine cytopathology is positive in 80% to 90% of patients with carcinoma in situ.

Carcinoma in situ is present in 25% or more of patients with high-grade superficial tumors (Koss et al, 1974), and between 40% and 83% progress to muscle-invasive cancer (Althausen et al, 1976). Carcinoma in situ occurs in 20% to 75% of high-grade muscle-invasive cancers. Patients with marked urinary symptoms generally have a shorter interval preceding the development of muscle-invasive cancer. About 20% of patients treated with cystectomy for diffuse carcinoma in situ are found to have microscopic muscle-invading cancer (Farrow et al, 1976).

A variety of investigative approaches have confirmed carcinoma in situ's direct relationship to muscle-invading cancer. Cytogenetic (loss of chromosome 17p) (Olumni et al, 1990 ; Tsai et al, 1990 ; Knowles et al, 1994), molecular genetic (Sarkis et al, 1993), and immunohistologic (Sarkis et al, 1993, 1994 [533] [534]; Esrig et al, 1994) studies have shown that high proportions of both carcinoma in

situ and deeply invasive bladder cancer have deletions and/or mutations of the TP53 gene and alterations of its protein product. This not only supports the contention that carcinoma in situ is a precursor lesion of invasive bladder cancer but also, to a large degree, eliminates it as a precursor of low-grade papillary tumors in which TP53 abnormalities are rarely found (except in extremely young patients) (Habuchi et al, 1992 ; Spruck et al, 1994 ; Linn et al, 1998).

Transitional Cell (Urothelial) Carcinoma

Tumor Architecture

More than 90% of bladder cancers are TCCs . At a consensus conference, the pathologists of the WHO and the ISUP preferred to term these urothelial cancers (Epstein et al, 1998); such a name may be confusing for nonpathologists because cancers of other histologic types, such as squamous cancers and adenocarcinomas, also arise in the urothelium. Regardless of name, urothelial (transitional cell) cancers differ from normal urothelium by having an increased number of epithelial cell layers with papillary foldings of the mucosa, loss of cell polarity, abnormal cell maturation from basal to superficial layers, increased nuclear-cytoplasmic ratio, prominent nucleoli, clumping of chromatin, and increased number of mitoses (Koss, 1975).

Urothelial carcinomas demonstrate a variety of patterns of tumor growth, including papillary, sessile, infiltrating, nodular, mixed, and flat intraepithelial growth (carcinoma in situ). Cancer invasion between and through the smooth muscle cells of the tunica muscularis mucosa

(within the lamina propria) can be mistaken for invasion of the bladder detrusor muscle (Younes et al, 1990 ; Engel et al, 1992), a particular problem in specimens obtained by endoscopic biopsy or transurethral curettage.

Urothelium has great metaplastic potential; therefore, urothelial carcinomas may contain spindle cell (Young et al, 1988), squamous, or adenocarcinomatous elements. These elements are present in about one third of muscle-invasive urothelial bladder cancers, and several may be exhibited in a single cancer. Approximately 70% of bladder tumors are papillary, 10% are nodular, and 20% are mixed.

Tumor Grading

No uniformly accepted grading system for bladder cancer exists. Most commonly used systems are based on the degree of anaplasia of the tumor cells (Broders, 1922 ; Bergkvist et al, 1965 ; Mostofi et al, 1973 ; Koss, 1975). In a consensus conference, the WHO and the ISUP decided to classify many of these tumors as papillary urothelial neoplasms (Epstein et al, 1998).

A strong correlation exists between tumor grade and stage (Jewett and Strong, 1946), with most well-differentiated and moderately differentiated tumors being superficial and most poorly differentiated ones being muscle invasive. Stage for stage, there is a significant correlation between tumor grade and prognosis; however, the correlation between tumor stage and prognosis is even stronger. As several authors (Knowles et al, 1994 ; Spruck et al, 1994 ; Reznikoff et al, 1996 ; Cote and Chatterjee, 1999) have proposed, there are now molecular and cytogenetic data to support the well-established clinical

impression that low-grade (all well-differentiated and most moderately differentiated) tumors and high-grade (poorly differentiated) tumors have fundamentally different origins, with the former losing one or more suppressor genes on chromosome 9q and the latter having TP53, RB, and/or P16 abnormalities as early events.

A papilloma (grade 0) is a papillary lesion with a fine fibrovascular core covered by normal bladder mucosa (Friedell et al, 1976 ; Cheng et al, 1999c) .It does not have more than seven epithelial cell layers nor any abnormalities in histology. This is an extremely rare tumor that, unlike TCCs, almost never recurs after endoscopic resection, so that if it occurs alone, it may legitimately be considered to be a benign neoplasm (Cheng et al, 1999c). However, it must be remembered that a histologic papilloma is often found in the same bladder as higher-grade urothelial cancer, clouding the certainty of its benignity. Molecular analyses of these lesions have not been reported.

Well-differentiated tumors have a thin fibrovascular stalk with a thickened urothelium containing more than seven cell layers, with cells exhibiting only slight anaplasia and pleomorphism. The disturbance of the base-to-surface cellular maturation is mild, and there are only rare mitotic figures. When they are mucosally confined, these have been termed papillary urothelial tumors of low malignant potential by the WHO and the ISUP (Epstein et al, 1998). However, even when detected alone, they often recur, and recurrences may be of higher histologic grade and stage (Cheng et al, 1999c). Lesions with this appearance (similar to those formerly called grade 1) are urothelial

cancers. They are found in the same bladders (and frequently in the same individual tumors) as higher-grade cancers (Cheng et al, 2000a), and share similar molecular (Cote and Chatterjee, 1999) and prognostic features with low-grade cancers (Cheng et al, 1999c ; Cheng and Bostwick, 2000 ; Oyasu, 2000).

Moderately differentiated (low grade—old grade 2) tumors have a wider fibrovascular core, a greater disturbance of the base-to-surface cellular maturation, and a loss of cell polarity. The nuclear-cytoplasmic ratio is higher, with more nuclear pleomorphism and prominent nucleoli. Mitotic figures are more frequent. These have been termed low-grade urothelial carcinomas in the new WHO and ISUP classification (Epstein et al, 1998). Murphy and colleagues (2002) point out the difficulties for even experienced practitioners to distinguish between low malignant potential and low-grade carcinoma lesions as defined in the current classification.

Poorly differentiated tumors, named high-grade urothelial carcinoma in the new WHO and ISUP system (Epstein et al, 1998) (old grade 3), have cells that do not differentiate as they progress from the basement membrane to the surface. Marked nuclear pleomorphism is noted, with a high nuclear-cytoplasmic ratio. Mitotic figures may be frequent (Friedell et al, 1980). The changes made in the new classification may allow grouping together of a larger number of patients who are at high risk for progression.

Metaplastic Elements

It is not unusual for different tumor types to coexist in the same

bladder; however, all epithelial tumors are believed to have a common ancestry in the transitional epithelium. The presence of these metaplastic elements (e.g., SCC and adenocarcinoma) in a lesion that is primarily a urothelial carcinoma does not change the principal classification of the tumor as a urothelial carcinoma.

Squamous Cell Carcinoma

Etiology

Considerable variability is noted in the prevalence of SCC of the bladder in different parts of the world. It accounts for only 1% of bladder cancers in England (Costello et al, 1984), 3% to 7% in the United States (Koss, 1975 ; Lynch and Cohen, 1995), but as many as 75% in Egypt (El-Bolkainy et al, 1981). About 80% of SCCs in Egypt are associated with chronic infection with S. haematobium. These cancers occur in patients who are, on the average, 10 to 20 years younger than patients with TCC. Bilharzial cancers are exophytic, nodular, fungating lesions that are usually well differentiated and have a relatively low incidence of lymph node and distant metastases. Whether the low incidence of distant metastases is due to capillary and lymphatic fibrosis resulting from chronic schistosomal infection (Ghoneim and Awad, 1980) or to the relatively low histologic grade (El-Bolkainy et al, 1981) of these tumors is not clear.

Nonbilharzial SCCs are usually caused by chronic irritation from urinary calculi, long-term indwelling catheters, chronic urinary infections, or bladder diverticula. As many as 80% of paraplegics with chronic infections and/or indwelling catheters have squamous changes

in the bladder, and about 5% develop SCC (Bahnson, 1997). Cigarette smoking has also been reported to be significantly associated with an increased risk of bladder SCC (Kantor et al, 1988). Male predominance is far less striking in SCC (1.3:1 to 1.7:1) (Lynch and Cohen, 1995). In general, its prognosis is poor because most patients have advanced disease at the time of diagnosis.

Histology

SCC consists, characteristically, of keratinized islands that contain eccentric aggregates of cells called squamous pearls. They may show varying degrees of histologic differentiation (Koss, 1975). Cytology has been of limited utility in the diagnosis of this tumor. In a small series of patients with SCC, urinary excretion of psoriasin, produced by the tumor, was found in all cases (Ostergaard et al, 1997). However, because this protein is also excreted in squamous metaplasia, it is unlikely that this test is specific enough to be used in the diagnosis or screening of SCC or in the monitoring of patients who have not undergone cystectomy.

Histologic differentiation more loosely correlates with prognosis, stage for stage, than it does with urothelial carcinomas, but grade and node status still predict subsequent metastases (Zaghloul, 1996). Particularly with bilharzial SCCs, bone is the most common site of distant metastases (Zaghloul, 1996). As with aggressive urothelial cancer, SCCs often have P16 and TP53 abnormalities (Cote and Chatterjee, 1999), although the mechanisms of gene silencing often differ between the two tumor types (Tsutsumi et al, 1998). Several

reports suggest that, stage for stage, the prognosis of SCC is comparable to that of TCC (Johnson et al,1976;Richie et al, 1976).

Adenocarcinoma

Adenocarcinomas account for less than 2% of primary bladder cancers (Kantor et al, 1988 ; Lynch and Cohen, 1995). They are classified into three groups: (1) primary vesical; (2) urachal; and (3) metastatic (Manunta et al, 2005). Adenocarcinomas also occur in intestinal urinary conduits, augmentations, pouches, and ureterosigmoidostomies (Husmann and Spence, 1990 ; Spencer and Filmer, 1991).

Primary Vesical Adenocarcinoma

Adenocarcinomas usually arise in the bladder base area or in the dome, but they can occur anywhere. It is the most common type of cancer in exstrophic bladders. These tumors develop in response to chronic inflammation and irritation (Nielsen and Nielsen, 1983 ; Bennett et al, 1984).

All histologic variants of enteric adenocarcinoma occur in the bladder. Most are mucin producing (Koss, 1975). Signet-ring carcinomas characteristically produce linitis plastica of the bladder (Choi et al, 1984; Sheldon et al, 1984; Blute et al, 1989a). Most adenocarcinomas are poorly differentiated and invasive. They are more commonly associated with cystitis glandularis than with carcinoma in situ.

The generally poor prognosis associated with adenocarcinomas is due primarily to their advanced stage at diagnosis. There is no evidence to indicate that, stage for stage, their prognosis is markedly

different from that of urothelial carcinoma.

Urachal Carcinoma

Urachal carcinomas are extremely rare tumors that arise outside the bladder, and they are usually adenocarcinomas, although they may be primary TCCs or SCCs and, rarely, even sarcomas. Urachal carcinomas have a sharp demarcation between the tumor and the adjacent bladder epithelium, with the tumor being located in the bladder wall beneath the normal epithelium (Mostofi, 1954). They may appear with a bloody or mucoid discharge from the umbilicus or produce a mucocele, occurring as a palpable mass. Many urachal tumors have stippled calcifications on radiographs (Brick et al, 1988 ; Narumi et al, 1988). Tumors invading the bladder lumen may produce mucus in the urine.

Patients with urachal carcinomas have a worse prognosis than do those with primary bladder adenocarcinomas (Mostofi, 1954). Histologically, these tumors exhibit wider and deeper infiltration of the bladder wall than expected, compromising the results of partial cystectomy (Kakizoe et al, 1983 ; Sheldon et al, 1984). Urachal carcinomas metastasize to iliac and inguinal lymph nodes, omentum, liver, lung, and bone (Sheldon et al, 1984).

Metastatic Adenocarcinoma

One of the most common forms of adenocarcinoma of the bladder is metastatic (or invasive) adenocarcinoma (Choi et al, 1984). The primary sites for these tumors include the rectum, stomach, endometrium, breast, prostate, and ovary (Klinger, 1951).

MATERIALS AND METHODS

Study was conducted from November 2007 to January 2010 in our department of urology. All patients with haematuria were evaluated and those having a bladder tumor included in the study. Initially few patients with tumors more than 6 cm were included in the study, but later tumors less than 5 cm only were studied.

Patients were first stabilised and intra venous fluids given , then blood sample taken for lab investigations and grouping - typing.The coagulation profile also checked. Patients who presented with clot retention were subjected to cystoscopic clot evacuation in the daycare cystoscopy room and a 22F urethral foley inserted and irrigation started.

When the patient has stabilized and the haematuria had settled down USG KUB was done again and the findings recorded. Cytology was done. When the Sr. Creatinine was normal CECT was taken.None of the patients in the study had refractory haematuria, haematuria settled down in a maximum of 2 days. Twelve patients required blood transfusion as their haemoglobin was less than 10 gms. None of the patients were in shock at the time of presentation.

USG was done in our department as we scan routinely for our out and in patients. Imaging was done with full bladder in longitudinal and transverse sections. The USG achine used is a B Type equipment with a 1.5x zoom.The probe can be used in 2.5/3.5/5 MHz mode. It is an electronic convex array

probe with a 60mm radius and a 60º scanning angle. The USG findings were recorded for data analysis to be done later.

CECT was done with PHILIPS 64 slice CT .Plain KUB images were acquired first then 80 ml of non ionic contrast was administered intra venously and CT KUB images were acquired at 30 seconds (Cortico medullary phase) and 150 seconds (excretory phase) as 0.625 mm continuous slices with 1mm reconstruction. The Pitch was 1. Then the patient is asked to wait for 30 min for bladder imaging. During this period the patient is made ambulant to permit the mixing of contrast with urine in the bladder. Screening cystogram is taken to make sure that the bladder is filled with contrast and also to check whether there is good mixing of the contrast. When a good homogenous cystogram is seen bladder imaging is done and images were acquired.

Virtual endoscopic reconstruction made at the workstation by volume rendering algorithm and multiplanar image reconstruction with the Philips brilliance extended view 2 software. It took upto 1 hour for reconstruction and interpretation. Virtual endoscopic examination of the ureters and pelvis was also done in addition to the bladder. There were no associated tumors of the pelvis or ureter reported in the patients involved in the study. The image interpretation and reporting was done by a single radiology assistant.

Conventional cystoscopy and tumor resection was done preferentially under Spinal anaesthesia. A preliminary cystoscopy was done using a 21F sheath and a 30 degree telescope. The site of tumor, relation to ureteric orifice,

size, morphology and suspicious areas suggesting CIS were noted. Areas appearing as “red velvety” patches were biopsied with Cup Biopsy forceps and were sent separately for analysis. Following which using a 24F sheath, a 30 degree telescope and TURP working element all grossly visible tumor were resected as much as possible and specimen stored to be sent seperately. Then cold cup biopsy forceps were used to take biopsy at multiple sites in the tumor bed for muscle sample and they sent in separate container for HPE. Obturator block was used in cases were tumor was involving the lateral wall. Haemostasis was secured with loop and/or ball electrode 22F three way urethral foley was inserted for irrigation which was removed the next day if returns were clear. Mitomycin C 40 mg in 40 ml of saline was given intra vesically and held for 1 hour in post op ward in small tumors which were completely resected. The procedure was done by a skilled urology assistant and the findings were recorded by the person who had operated and were later collected for analysis.

The data were collected in the proforma sheet (model given in appendix) for analysis from the USG, Virtual endoscopic and conventional cystoscopic reporting.As there were no tumors in the upper tract there is no data for analyzing the sensitivity of virtual endoscopy in these context. So data collection was pertaining only for virtual cystoscopic evaluation. The following data were collected:

1. Site: There are 6 possible sites within the bladder where a tumor can arise. They are anterior, posterior, dome, right and left lateral wall, and base.

2. Size: largest diameter was taken

3. Morphology: sessile or papillary

4. Number of the tumors

Sensitivity of USG and Virtual cystoscopy in detecting lesions of various sizes was determined and compared with Conventional cystoscopic findings.

Also the final Histopathology of the tumor recorded.

OBSERVATION AND RESULTS

Totally 106 patients were evaluated.

Of these 54 patients were included in the study as they had a bladder tumor detected by cystoscopy and/or Ultrasonography and/ or Virtual cystoscopy or there were no tumor.Those patients who had no tumor on conventional cystoscopic examination comprised the true negative group. Those lesions present on cystoscopic examination but absent on USG or Virtual cystoscopy are considered to have been missed by the above imaging modality and represent the false negative group respectively. Those lesions detected on USG and VC but not present on Conventional cystoscopy were considered as false positives for the respective imaging study. Of the 54 patients 38 had a bladder tumor on conventional cystoscopy and 16 didn’t have. Two of the bladder tumors were recurrent bladder tumors (patient 17 and 30). Of the 16 patients 10 were reported to contain a bladder tumor by USG and/or VC, they comprise the false positives. Whereas 6 patients had no lesion detected by imaging and by conventional cystoscopy.

About 10 patients were were excluded from the study as they had raised renal parameters. And further 13 patients were excluded as they had large bladder growths(> 5 cm).

Patients who were found to have causes other than bladder tumor in the study were:

1. Vesical calculus :3 patients
2. Renal stone : 10 patients
3. Ureteric stones : 5 patients
4. BPH : 13 patients
5. Carcinoma of prostate : 2 patients
6. UTI : 9 patients
7. Renal cell carcinoma : 5 patients
8. Coagulopathy : 5 patients
    - 3 were on heparin treatment for deep vein thrombosis
    - 1 was on aspirin therapy for Ischemic heart disease
    - 1 was a patient on heparin treatment for post traumatic illiac artery thrombosis

DESCRIPTIVE STATISTICAL DATA

Sex Distribution :

Gender	Frequency (n)	Percent (%)
Male	38	70.4
Female	16	29.6
Total	**54**	**100.0**

Of the 54 patients in the study 38 (70.4 %) were males and 16 (29. 6 %) females.

AGE DISTRIBUTION

Age group	Frequency (n)	Percent (%)
Up to 45yrs	2	3.7
46 - 50yrs	14	25.9
51 - 55yrs	14	25.9
56 - 60yrs	16	29.6
61yrs and above	8	14.9
Total	**54**	**100.0**

Most of the patients were in the age group of 46 to 60 years.

GENDER AND AGE DISTRIBUTION

Gender Vs Age group	Male		Female	
	n	%	n	%
Upto 45yrs	2	5.3	0	0.0
46 - 50yrs	10	26.3	4	25.0
51 - 55yrs	12	31.6	2	12.5
56 - 60yrs	8	21.1	8	50.0
61yrs and above	6	15.8	2	12.5
Total	**38**	**100.0**	**16**	**100.0**

In males the most frequent age group is 51 – 55 years where as in females it is 56 – 60 years.

Age (yrs)	N	Minimum	Maximum	Mean	Std. Deviation
Male	38	43	72	54.03	6.378
Female	16	46	63	55.37	5.667
Total (Both)	54	43	72	54.43	6.154

The minimum age is 43 years and the maximum was 72 years.

Of the 54 patients 20 patients had microscopic haematuria on evaluation and 34 presented with gross haematuria. All the 20 patients with microscopic haematuria the main presenting complaint was storage (irritative) LUTS.

Of the 38 of 54 patients with bladder tumor 51 bladder tumors were detected as five of them had multiple bladder tumors.

Of the 51 bladder tumors only 3 of them were larger than 5 cm as we preferred to evaluate lesions less than 6 cm. One of the large bladder tumor was the first patient and after which we decided not to evaluate these large tumors as there was no use. Other two were special cases, one was a adenocarcinoma and other was a mesenchymal tumor of the bladder.

SITE DISTRIBUTION OF THE TUMOR

Site	Frequency (n)	Percent (%)
Anterior	18	35.3
Posterior	13	25.5
Base	4	7.8
Dome	5	9.8
L lateral	5	9.8
R lateral	6	11.8
Total	**51**	**100.0**

Most of the tumors were located in the anterior wall (18 / 51) and the posterior wall (13 / 51).

MORPHOLOGY DISTRIBUTION

Papillary / Sessile	Frequency (n)	Percent (%)
Papillary	42	82.4
Sessile	9	17.6
Total	**51**	**100.0**

Most of the tumors were papillary (82. 4 %) type, probably as we included small sized tumors in the study.

DIAGNOSTIC TEST EVALUATION

Ultrasonography Vs Conventional Cystoscopy

		Conventional Cystoscopy		Total
		Positive	**Negative**	
Ultra sonography	Positive	25	7	**32**
	Negative	26	9	**35**
Total		**51**	**16**	**67**

P.Value = **0.713 (Not significant)**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	49.02%	(35.86, 62.32)
Specificity	56.25%	(33.18, 76.90)
Positive Predictive Value	78.13%	(61.24, 88.98)
Negative Predictive Value	25.71%	(14.16, 42.07)
Diagnostic Accuracy	50.75%	(39.06, 62.35)

Ultrasound was found to have an sensitivity of 49.02 % as it detected 25 / 51 tumors. All the missed lesions 26/51 were less than 3 cm . Missed lesions were located in the anterior wall (15/26 = 57.69 %) , posterior wall (7/ 26 = 26.92 %) and dome (4/26). Smaller lesions in lateral walls were detected. So ultrasound is not a sensitive tool for detecting lesions less than 3 cm in the anterior and posterior bladder wall. This is probably due to the reverberation artifact.

VIRTUAL CYSTOSCOPY VS CONVENTIONAL CYSTOSCOPY

		Conventional Cystoscopy		Total
		Positive	**Negative**	
Virtual Cystoscopy	Positive	47	3	**50**
	Negative	4	13	**17**
Total		**51**	**16**	**67**

P.Value = **<0.001 (Significant)**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	92.16%	(81.50, 96.91)
Specificity	81.25%	(56.99, 93.41)
Positive Predictive Value	94.00%	(83.78, 97.94)
Negative Predictive Value	76.47%	(52.74, 90.45)
Diagnostic Accuracy	89.55%	(79.97, 94.85)

Virtual cystoscopy had a sensitivity of 92.16 % as it detected 47 of 51 tumors. And further analysis were done for sensitivity of the imaging modalities for tumor size less than / equal to 1 cm and more than 1 cm.

Size of the lesion is less than or equal to 1 cm (Ultrasound)

		Conventional Cystoscopy		Total
		Positive	**Negative**	
Ultra sonography	Positive	0	7	**7**
	Negative	21	9	**30**
Total		**21**	**16**	**37**

P.Value = **0.003 (Significant)**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	0.0%	(0.0, 15.46)
Specificity	56.25%	(33.18, 76.90)
Positive Predictive Value	0.0%	(0.0, 35.43)
Negative Predictive Value	30.00%	(16.66, 47.88)
Diagnostic Accuracy	24.32%	(13.36, 40.12)

Ultrasound was unable to detect tumors less than/equal to 1cm.

Size of the lesion is less than or equal to 1 cm (Virtual Cystoscopy)

		Conventional Cystoscopy		**Total**
		Positive	**Negative**	
Virtual Cystoscopy	Positive	17	3	**20**
	Negative	4	13	**17**
Total		**21**	**16**	**37**

P.Value = **<0.001 (Significant)**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	80.95%	(60.00, 92.33)
Specificity	81.25%	(56.99, 93.41)
Positive Predictive Value	85.00%	(63.96, 94.76)
Negative Predictive Value	76.47%	(52.74, 90.45)

Sensitivity falls down when the size of the lesion is below 1 cm.

RESULTS: SIZE OF THE LESION IS MORE THAN 1 CM

Ultrasound:

		Conventional Cystoscopy		Total
		Positive	**Negative**	
Ultra sonography	Positive	25	0	**25**
	Negative	5	0	**5**
Total		**30**	**0**	**30**

P.Value = **Not possible**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	83.33%	(66.44, 92.66)
Specificity	--	
Positive Predictive Value	100%	(86.68, 100)
Negative Predictive Value	0.0%	(0.0, 43.45)
Diagnostic Accuracy	83.33%	(66.44, 92.66)

Sensitivity improves when the size is more than 1cm. (83. 33 %)

Virtual Cystoscopy :

		Conventional Cystoscopy		Total
		Positive	**Negative**	
Virtual Cystoscopy	Positive	30	0	**30**
	Negative	0	0	**0**
Total		**30**	**0**	**30**

P.Value = **Not possible**

Parameter	**Estimate**	**95% CIs Lower - Upper**
Sensitivity	100%	(88.65, 100)
Specificity	--	
Positive Predictive Value	100%	(88.65, 100)
Negative Predictive Value	--	
Diagnostic Accuracy	100%	(88.65, 100)

Virtual cystoscopy detects all the tumors above 1 cm in size.

Carcinoma in situ was present in 5 patients and Virtual cystoscopy was not able to identify it. In these patients 4 had a positive cytology.

Of the 38 patients who had bladder tumor only 6 patients had a positive cytology with a sensitivity of only 15.78 %.

TURBx (Trans - urethral resection biopsy) was done in two patients where some residual tumor was left unresected. One was a transitional cell carcinoma and other adenocarcinoma of the bladder with obvious T3 stage.

One patient had a partial cystectomy done. The patient presented as a mass abdomen and initially thought to arise from the uterus. It was an intra mural growth of bladder and cystoscopy revealed the mucosa to be intact over the growth. So a Trans – abdominal trucut biopsy was done and later the patient taken for partial cystectomy believing it to be a leiomyoma of bladder. Final specimen on immunohistochemical analysis revealed it as a mesenchyal tumor.

Rest of the patients was subjected to TURBT (Trans- urethral resection of bladder tumor) where all the grossly visible tumor was resected. Two of the resected tumors were found to be benign, chronic cystitic changes. Rests were transitional cell carcinoma.

DISCUSSION

Virtual cystoscopy has a high sensitivity, 92.16 % and 100 % sensitivity to tumors more than 1 cm. But this is still inferior to conventional cystoscopy. Also it misses out carcinoma in situ. This can be overcome by combining cytology with it. Although cytology by it self has poor sensitivityfor low grade tumor it has high sensitivity for high grade lesions like CIS. Table below sums up the results of the study.

	Sensitivity
Cytology	15.78 %
USG	49.02 %
Virtual cystoscopy	92.16 %

So it appears that virtual cystoscopy is not sensitive enough to replace conventional cystoscopy. So we need other modalities for screening for urothelial tumors. Lots of work is currently focused on olecular markers. Hence in the future we have to rely on molecular markers for avoiding unnecessary cystoscopy in those patients who don’t have a urothelial tumor.

Role of molecular was emphasized by **Bryan et al , Goodison et al and Ehdaie et al** "Molecular markers will become increasingly important for urothelial cancer diagnosis and prognostication as we continue through the century, with both conventional and novel experimental platforms providing robust and reproducible assays with high sensitivity and specificity, and point-of-care utility.

(Bryan RT, Zeegers MP, James ND, Wallace DM, Cheng KK. Biomarkers in bladder cancer. *BJU Int* 2010; **105** : 608– 1311.

Goodison S, Rosser CJ, Urquidi V. Urinary proteomic profiling for diagnostic bladder cancer biomarkers.*Expert Rev Proteomics* 2009; **6** : 507–14.

Ehdaie B, Theodorescu D. Predicting tumor outcomes in urothelial bladder carcinoma: turning pathways into clinical biomarkers of prognosis. *Expert Rev Anticancer Ther* 2008;**8** : 1103–10).

I close this discussion with the quote “Finally, we think that cystoscopy will remain the ‘gold standard’ for ruling out bladder cancer in the haematuria patient as of now. However, conventional white light cystoscopy will evolve to embrace new imaging technologies with improved capabilities, such as narrow band and optical coherence tomography.”

-Richard T. Bryan and Michael A. Wallace,

Bladder Cancer Prognosis Programme Bladder

Cancer Prognosis Programme,

University of Birmingham, UK

Cystoscopy is easy to teach, familiar to all urologists, reasonably accurate and performed with low morbidity around the world. It is performed in minutes, in contrast to virtual cystoscopy, which takes time.

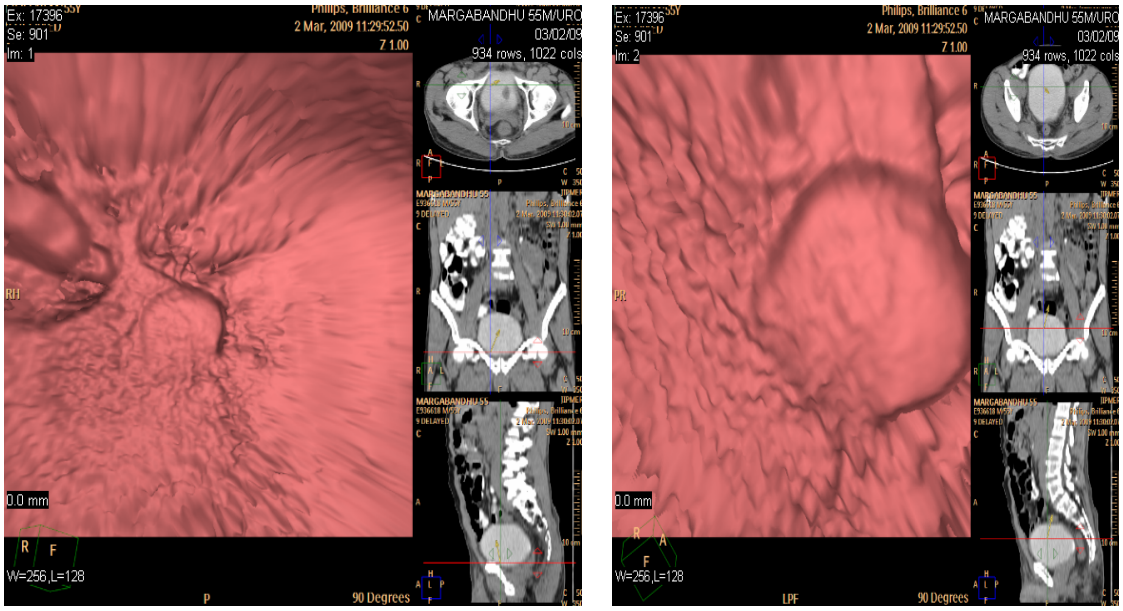
CONCLUSION

Despite the obvious benefits of virtual cystoscopy in terms of less invasiveness and more comfort to the patient, it has several limitations. These include,

1. Low detection rate for lesions smaller than 1 cm
2. Not able to detect CIS.
3. Inferior to conventional cystoscopy in detecting bladder lesions.

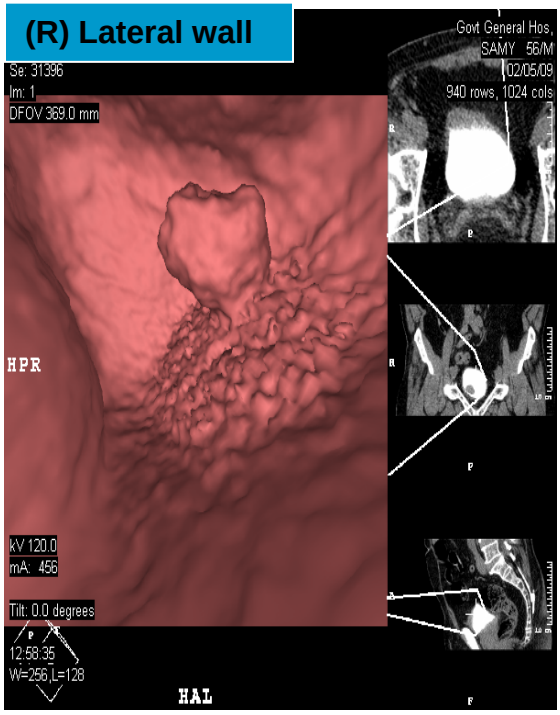
So Virtual cystoscopy cannot replase conventional cystoscopy. It may have a place in the evaluation of patients with haematuria in stricture disease and surgically poor risk patients.

Sessile lesion (L), Lateral wall

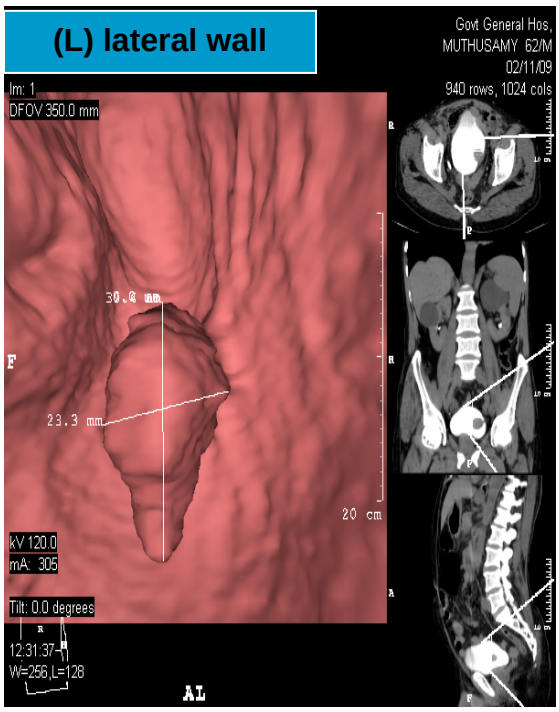


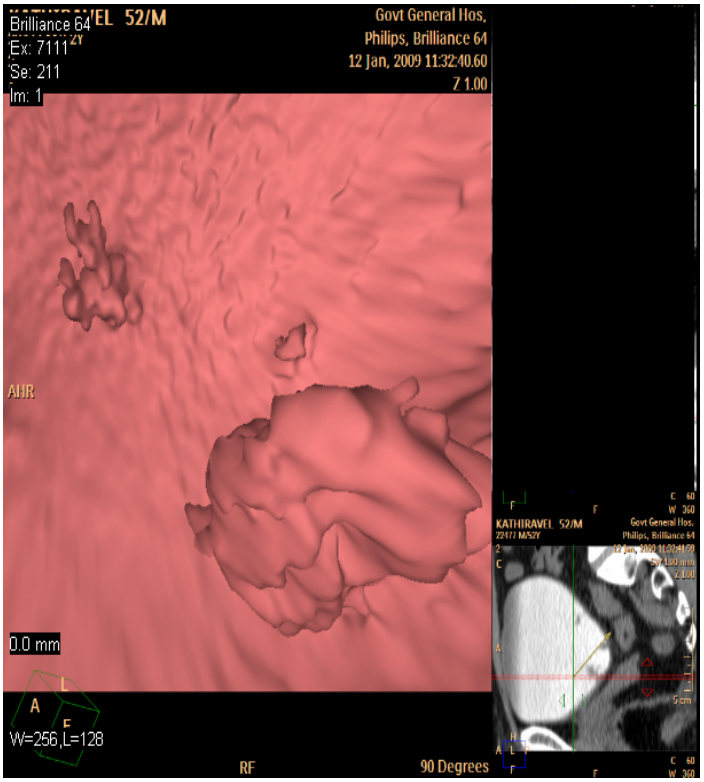
Pedunculated tumor

(R) Lateral wall

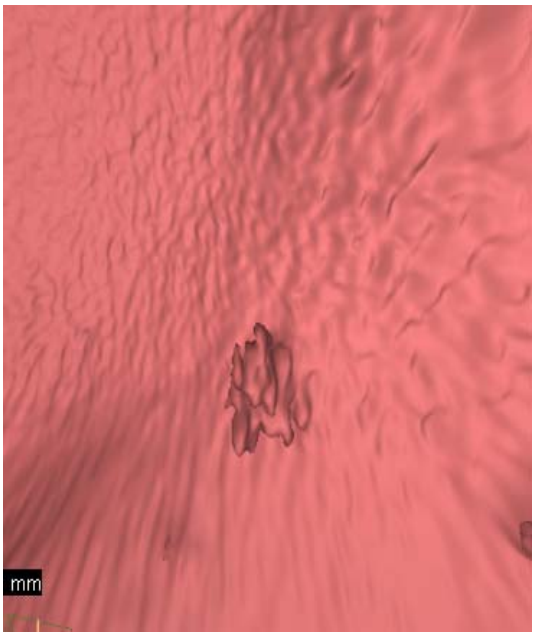


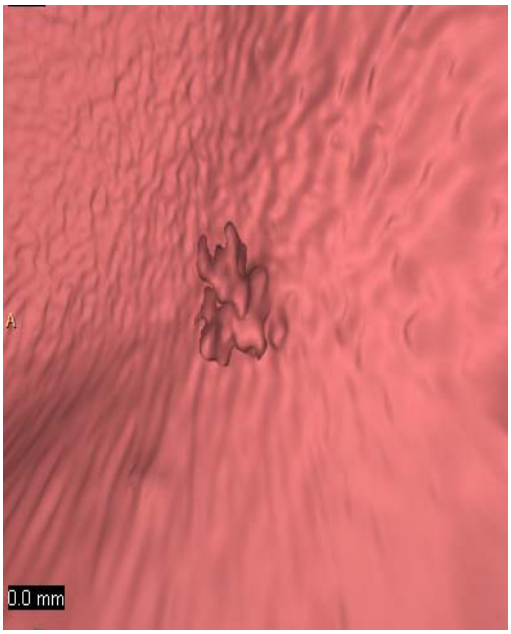
(L) lateral wall



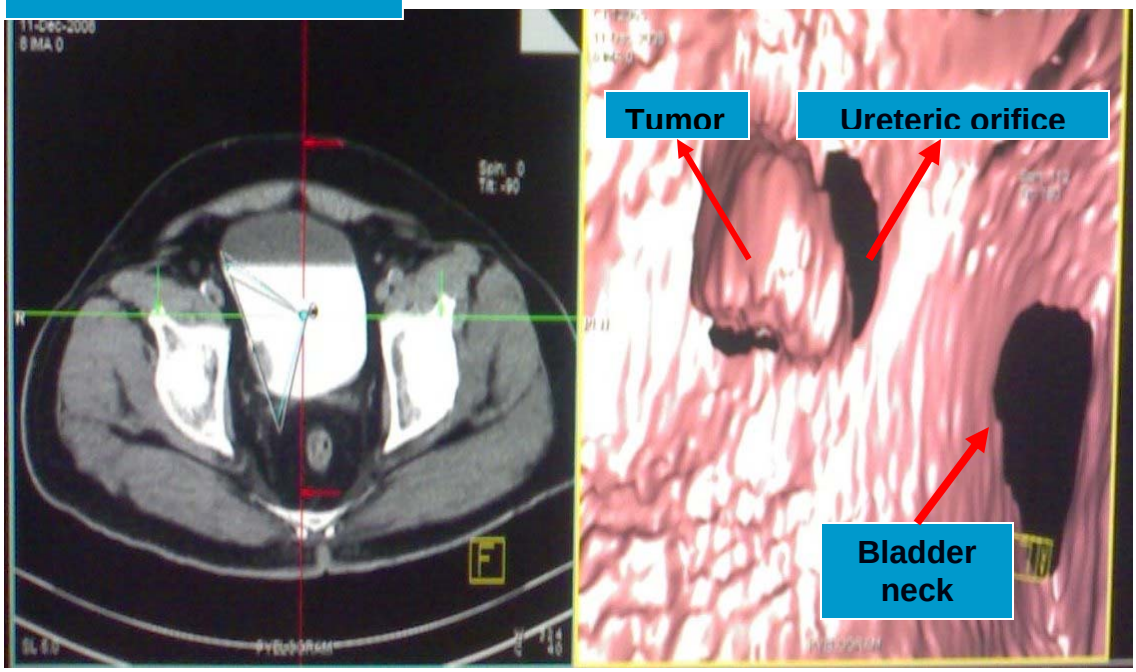


Multiple - Small tumors
Posterior wall of bladder

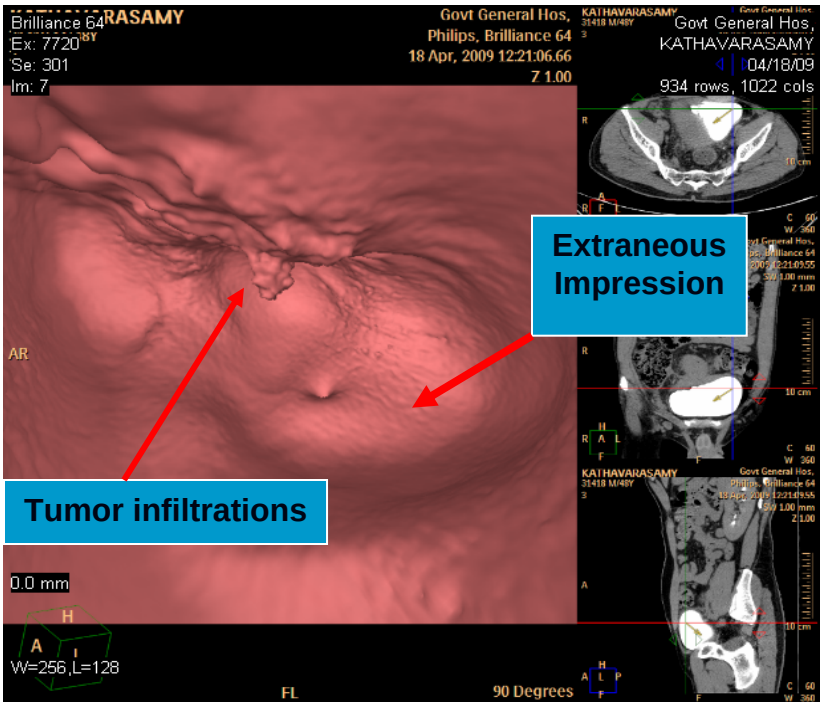




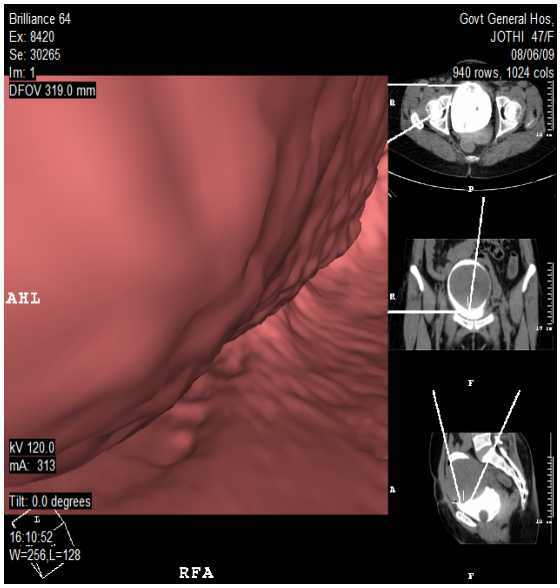
R Ureteric orifice tumor

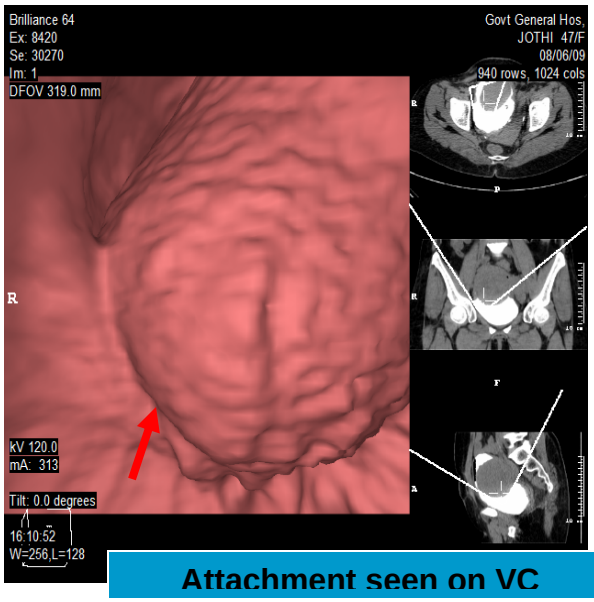


Sigmoid growth infiltrating the bladder (Adenocarcinoma)



Large mesenchymal tumor- appeared to be extrinsic

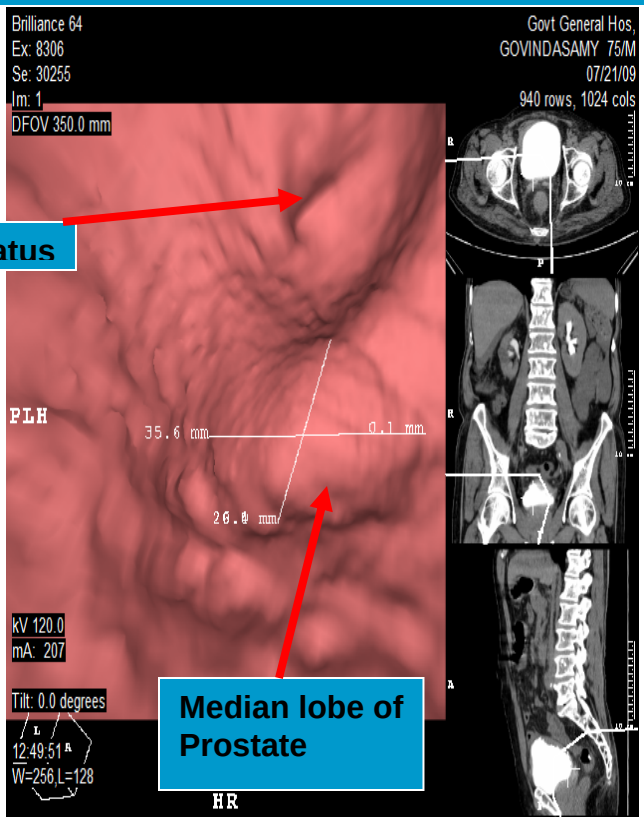




Attachment seen on VC

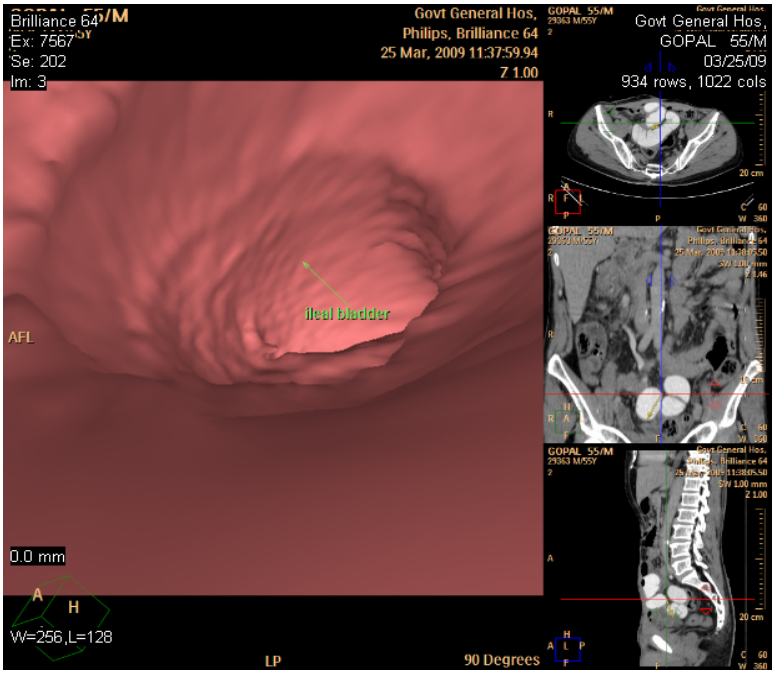
Doubtful Tumor near bladder neck – Median lobe of prostate

Internal meatus

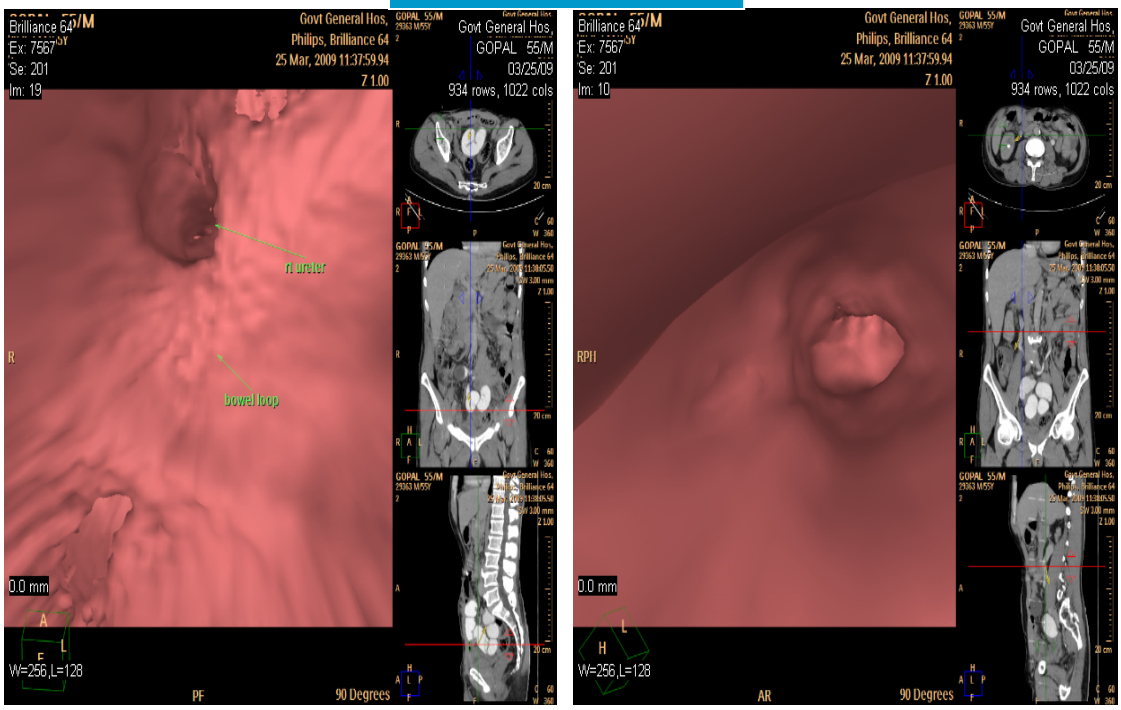


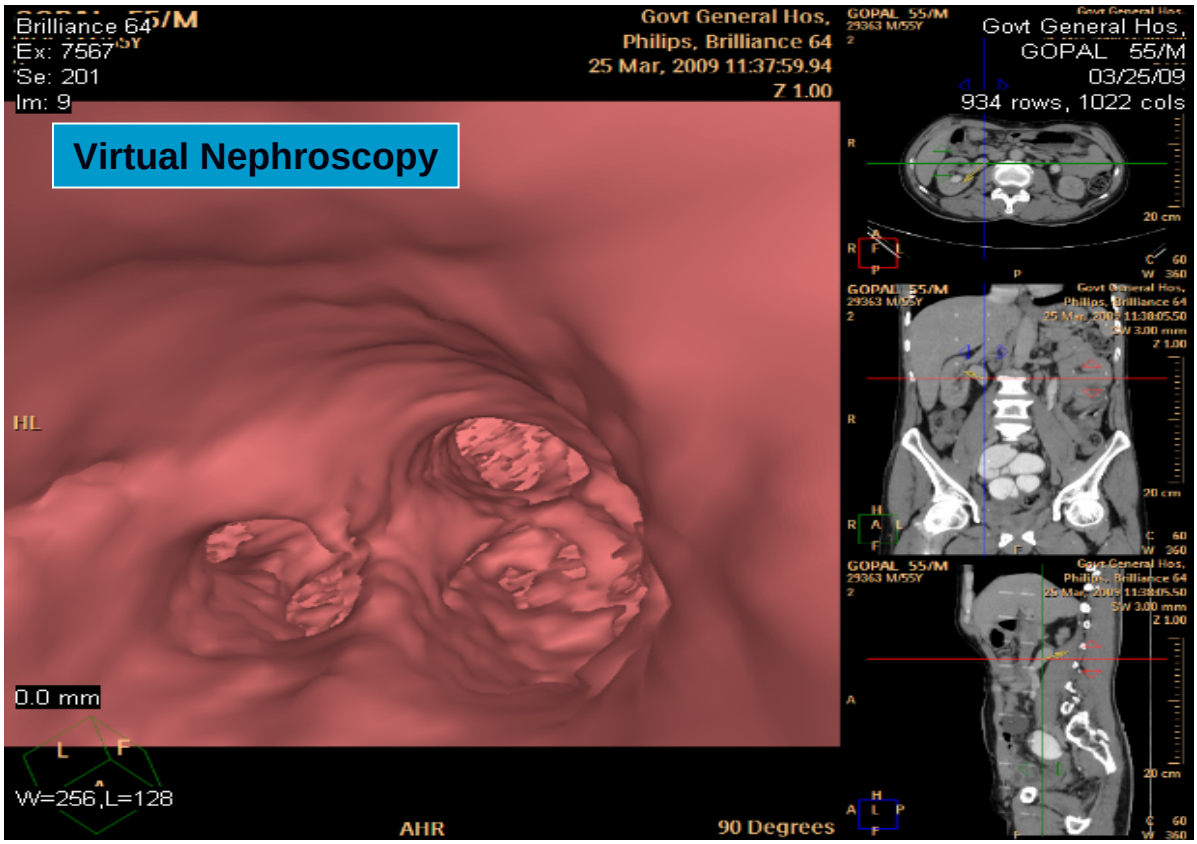
Median lobe of Prostate

Post radical cystectomy patient - on illeal bladder diversion



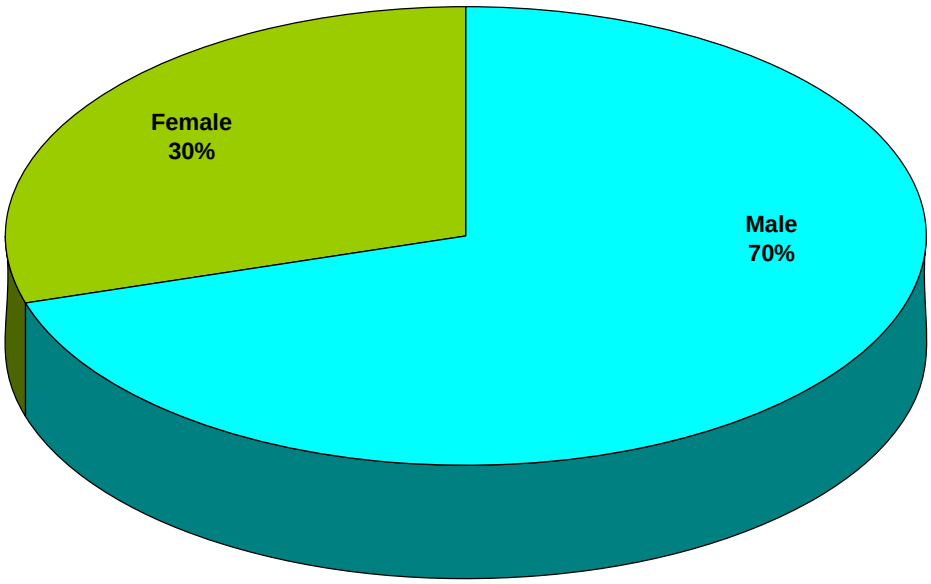
Virtual Ureteroscopy



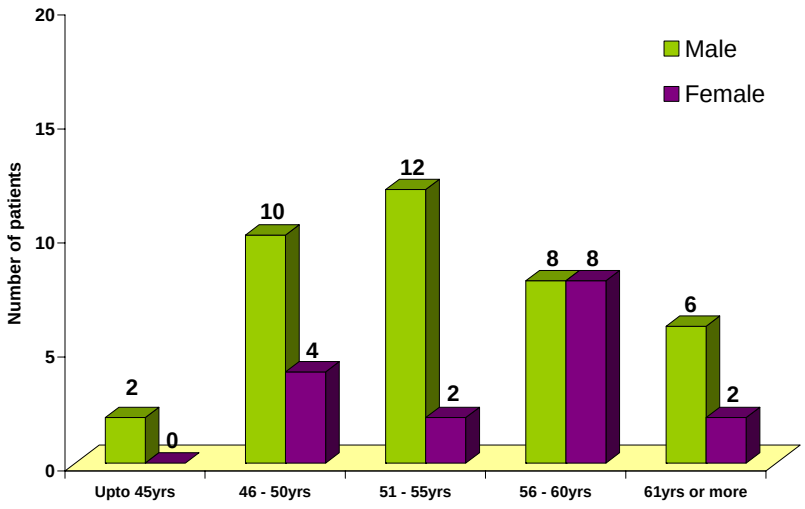


iCharts

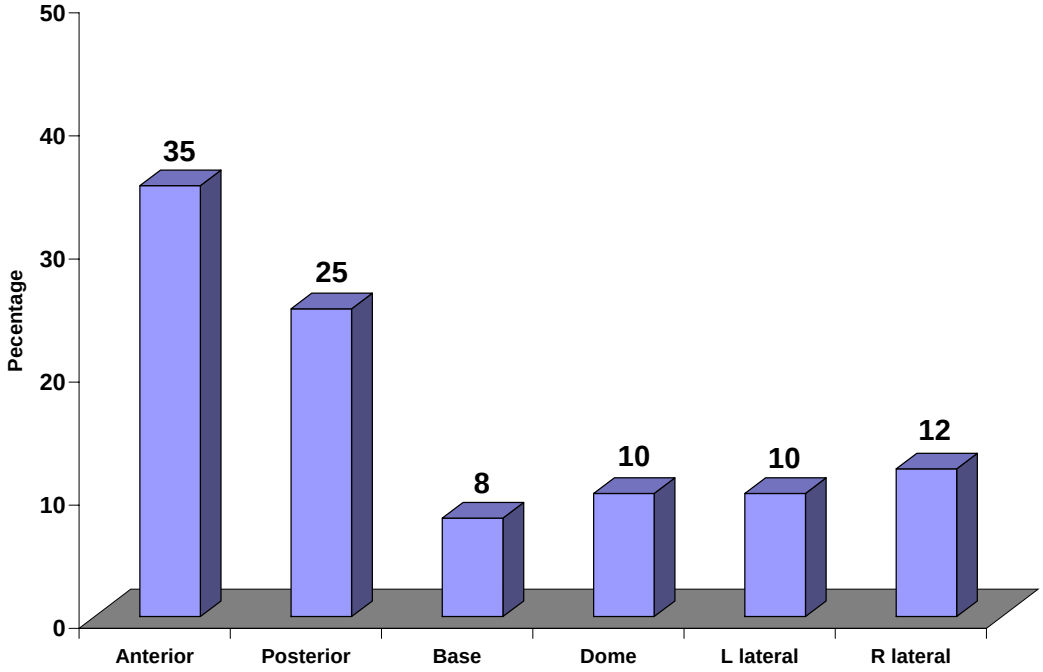
Male female Ratio



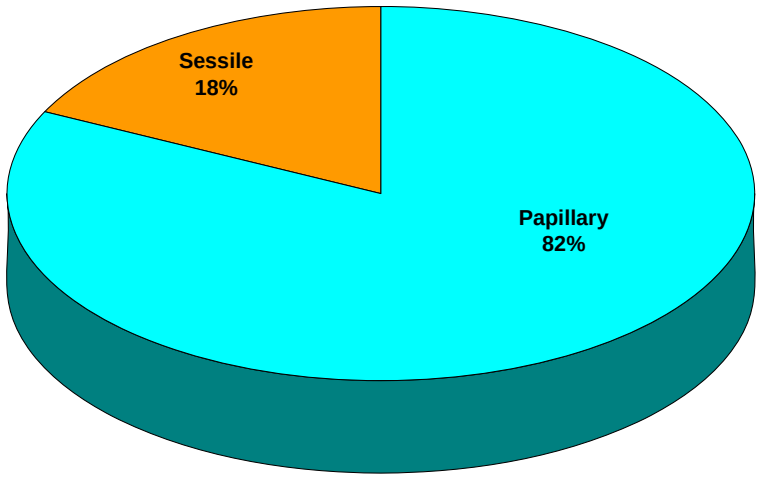
Age sex Distribution



Site Distribution

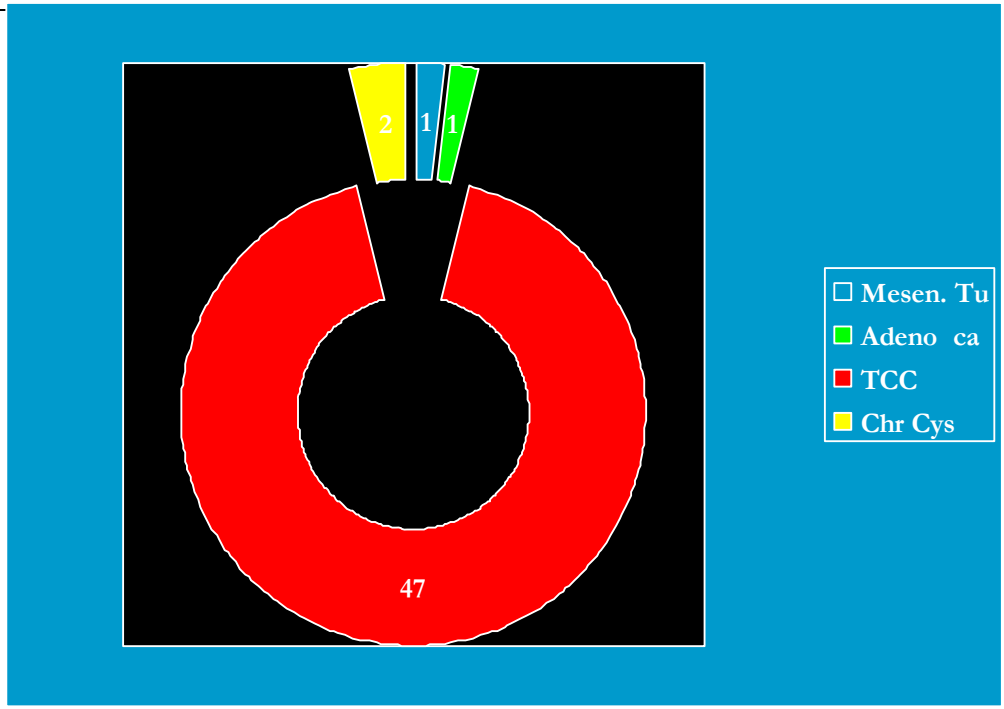


Morphology distribution



Histopathological break up :

i



GLOSSARY

USG	:	Ultrasound/Ultrasonogram
KUB	:	Kidney, Ureter and Bladder
VE	:	Virtual endoscopy
VC	:	Virtual cystoscopy
CECT	:	Contrast enhanced CT
CT	:	Computerised tomogram
CIS	:	Carcinoma in Situ
LUTS	:	Lower urinary tract symptoms
1	:	Positive (+)
0	:	Negative (-)
TURBT	:	Transurethral resection of bladder tumor
TURBx	:	Transurethral resection biopsy
TCC	:	Transitional cell carcinoma
Ch CYS	:	Chronic cystitis
Adeno CA	:	Adenocarcinoma
Mesen T	:	Mesenchymal tumor

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PROFORMA

NAME:

AGE: SEX:

ADDRESS:

CONTACT NUMBER:

IP NO: OP NO:

PRESENTING COMPLAINTS:

PHYSICAL EXAMINATION:

INVESTIGATION:

1.URINE:

ALBUMIN

SUGAR

DEPOSITS

2.URINE CULTURE AND SENSITIVITY:

3.HAEMOGRAM:

HB
TC
DC
ESR

4.URINE CYTOLOGY:

5.USG KUB:

(R) KIDNEY:

(L) KIDNEY:

BLADDER:

Number of Lesion site size
morphology

6.VIRTUAL ENDOSCOPY FINDINGS:

Number of Lesion site size
morphology

7. CONVENTIONAL ENDOSCOPY FINDINGS:

Number of Lesion site size
morphology

8.HISTOPATHOLOGY REPORT :

9.COMMENTS:

CONSENT FORM

I have clearly understood the need for the investigation **VIRTUAL ENDOSCOPY** from the doctor. I also understand that this investigation is being done for the evaluation of blood in the urine. I was also explained that a CT scan will be taken, which need exposure to X- rays and an intra- venous contrast agent will be injected. I was also explained the side effects of the X-rays and the contrast agent. Having fully understood the implications I consent for the above investigation whole heartedly

(Signature of the Patient)

patient	age	sex	Haematuria	leison	site	size (cm)	papillary/sessile	USG +/ -	VC + / -	Cytology +/-	CIS	Surgery	HPE
1	45	M	gross	1	R lateral	6	sessile	1	1	1	0	TURBx	TCC
				2	Dome	1	papillary	0	1			TURBT	TCC
				3	anterior	0.5	papillary	0	1			TURBT	TCC
				4	anterior	0.5	papillary	0	1			TURBT	TCC
2	50	M	gross	1	posterior	4	papillary	1	1	0	0	TURBT	TCC
3	47	M	gross	1	anterior	5	sessile	1	1	0	0	TURBT	TCC
4	60	M	gross	1	l lateral	4	papillary	1	1	0	0	TURBT	TCC
5	54	M	gross	1	l lateral	3.5	papillary	1	1	0	0	TURBT	TCC
6	65	M	microscopic	1	Dome	2.5	papillary	0	1	0	0	TURBT	TCC
7	46	M	gross	1	anterior	1	papillary	0	1	0	0	TURBT	TCC
8	47	F	gross	1	R lateral	4	sessile	1	1	0	0	TURBT	TCC
9	51	M	gross	1	anterior	5	sessile	1	1	0	0	TURBT	TCC
10	53	M	gross	1	l lateral	4	sessile	1	1	1	1	TURBT	TCC
				2	anterior	1	papillary	0	1			TURBT	TCC
				3	anterior	0.5	papillary	0	0			TURBT	TCC
				4	anterior	0.5	papillary	0	1			TURBT	TCC
				5	anterior	0.4	papillary	0	0			TURBT	Ch. CYS
11	58	M	gross	1	R lateral	4	sessile	1	1	1	1	TURBT	TCC
12	61	M	gross	1	R lateral	6	sessile	1	1	0	0	TURBx	Adeno CA
13	59	F	gross	1	posterior	2.5	papillary	1	1	1	1	TURBT	TCC
				2	posterior	1	papillary	0	1			TURBT	TCC
				3	posterior	0.5	papillary	0	1			TURBT	TCC
				4	posterior	0.5	papillary	0	1			TURBT	TCC
14	54	M		1	l lateral	2.8	papillary	1	1	0	0	TURBT	TCC
15	51	M	microscopic	1	posterior	1	papillary	0	1	0	0	TURBT	TCC
16	47	M	microscopic	1	anterior	1	papillary	0	1	0	0	TURBT	TCC
17	46	F	gross	1	posterior	3.5	papillary	1	1	0	0	TURBT	TCC
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19	55	M	gross	1	Base	2.5	papillary	1	1	0	0	TURBT	TCC
20	61	F	gross	1	Dome	1	papillary	0	1	0	0	TURBT	TCC
21	63	M	gross	1	posterior	2.5	papillary	1	1	0	0	TURBT	TCC
22	46	M	gross	1	posterior	4.5	sessile	1	1	1	1	TURBT	TCC
				2	anterior	1	papillary	0	1			TURBT	TCC

patient	age	sex	Haematuria	leison	site	size (cm)	papillary/sessile	USG +/ -	VC + / -	Cytology +/-	CIS	Surgery	HPE
				3	anterior	0.5	papillary	0	0			TURBT	TCC
23	51	M	gross	1	anterior	1	papillary	0	1	0	0	TURBT	TCC
24	60	F	gross	1	Base	2.5	papillary	1	1	0	0	TURBT	TCC
25	55	M	gross	1	Base	1.8	papillary	1	1	0	0	TURBT	TCC
26	72	M	gross	1	Base	2.2	papillary	1	1	0	0	TURBT	TCC
27	47	F	microscopic	1	Dome	8	sessile	1	1	0	0	Par. Cys	Mesen. T
28	49	M	gross	1	R Lateral	1.8	papillary	1	1	0	0	TURBT	TCC
29	58	M	gross	1	Posterior	1.5	papillary	0	1	0	0	TURBT	TCC
30	59	F	gross	1	Dome	1.7	papillary	0	1	0	0	TURBT	TCC
31	65	M	gross	1	Anterior	1.6	papillary	0	1	0	0	TURBT	TCC
32	47	F	gross	1	Anterior	1.5	papillary	0	1	0	0	TURBT	TCC
33	49	M	gross	1	Posterior	2.5	papillary	1	1	0	0	TURBT	TCC
			gross	2	Anterior	0.5	papillary	0	0			TURBT	Chr. CYS
34	53	M	microscopic	1	Anterior	1.8	papillary	1	1	0	1	TURBT	TCC
35	51	M	microscopic	1	Posterior	1	papillary	0	1	0	0	TURBT	TCC
36	60	M	gross	1	R Lateral	1.6	papillary	1	1	0	0	TURBT	TCC
37	59	F	gross	1	L Lateral	2.7	papillary	1	1	1	0	TURBT	TCC
38	58	F	microscopic	1	Posterior	1	papillary	0	1	0	0	TURBT	TCC
39	56	M	microscopic	0	NA	NA	NA	1	0	0	0	NA	NA
40	54	F	microscopic	0	NA	NA	NA	0	0	0	0		NA
41	57	F	gross	0	NA	NA	NA	0	0	0	0		NA
42	60	M	microscopic	0	NA	NA	NA	1	0	0	0		NA
43	49	M	microscopic	0	NA	NA	NA	0	1	0	0		NA
44	52	M	microscopic	0	NA	NA	NA	1	0	0	0		NA
45	47	F	gross	0	NA	NA	NA	0	0	0	0		NA
46	56	M	microscopic	0	NA	NA	NA	1	0	0	0		NA
47	52	M	microscopic	0	NA	NA	NA	0	0	0	0		NA
48	59	F	microscopic	0	NA	NA	NA	0	0	0	0		NA
49	61	M	microscopic	0	NA	NA	NA	1	0	0	0		NA
50	63	F	microscopic	0	NA	NA	NA	1	0	0	0		NA
51	49	M	microscopic	0	NA	NA	NA	0	1	0	0		NA
52	43	M	microscopic	0	NA	NA	NA	0	1	0	0		NA
53	50	M	microscopic	0	NA	NA	NA	0	0	0	0		NA

patient	age	sex	Haematuria	leison	site	size (cm)	papillary/sessile	USG +/ -	VC + / -	Cytology +/-	CIS	Surgery	HPE
54	57	F	microscopic	0	NA	NA	NA	1	0	0	0		NA